Clinical Consequences Associated with Catheter-related Deep Vein Thrombosis

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The faculty reported no conflict of interest related to this presentation.

Learning Objectives

• Describe the association between catheter-related thrombosis and bloodstream infection
• Discuss clinical consequences associated with UEDVT and impact on patient outcomes:
  • Infection
  • Pulmonary embolus
  • Pulmonary hypertension
  • Paradoxical stroke
  • Superior vena cava syndrome
  • Post-thrombotic syndrome
Part 1: Thrombosis and Infection

**Purpose**

To recognize the strong connection between infection and thrombosis

**Observations**

- Thrombosis begets infection
- Infection begets thrombosis

Thrombosis and Infection

**Observations**

- Adsorbed blood components on prosthetic surfaces facilitate adhesion and colonization of bacteria
- $^{111}$Indium *Staphylococcus epidermidis* sequestered to adherent thrombi
- SEM showed *S. epidermidis* adherent to fibrin (not passively trapped)

Thrombosis Enhances Infection

Mohammed SF et al. ASAIO Journal 2000;46:S63-68.

None

Platelet Inhibition

Anticoagulation

Effect of Platelet Inhibition and Anticoagulation

Interaction of *S. epidermidis* with Adherent Thrombus

Mohammed SF et al. ASAIO Journal 2000;46:S63-68.
Thrombosis Enhances Infection

Interaction of *S. epidermidis* with Fibrin

Is there clinical correlation?

Thrombosis Enhances Infection

**Interaction of *S. epidermidis* with Fibrin**

**Is there clinical correlation?**

Mohammad S F et al. 

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Etiology of Catheter-Associated Sepsis
Correlation With Thrombogenicity
Richard M. Stillman, MD; Fawzi Soliman, MD; Luis Garcia, MD; Phillip N. Sawyer, MD

- 94 central venous catheters
- Culture and sensitivity and inspection for thrombus upon removal
- Catheters removed when:
  - No longer needed
  - Thrombosed
  - Death of patient (rare)
- None removed for evidence of sepsis

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Etiology of Catheter-Associated Sepsis
Correlation With Thrombogenicity

**Results**

<table>
<thead>
<tr>
<th>Thrombus</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>30</td>
<td>53</td>
</tr>
</tbody>
</table>

Thrombus present: 100% of culture-positive catheters
36% of culture-negative catheters

\( p < 0.001 \)


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The Relationship Between the Thrombotic and Infectious Complications of Central Venous Catheters

**Purpose**
To assess the frequency of thrombotic and infectious complications of long-term use of central catheter in cancer patients.

**Methods**
- 16-month study period
- 72 autopsied patients
- Postmortem examinations of catheterized veins versus control (non-catheterized) veins
- Observations: Catheters sheathed in fibrin; Staph adheres to fibrin and produces enzymes that promote thrombogenesis

**Results**

<table>
<thead>
<tr>
<th>Thrombus</th>
<th>Yes (N=31)</th>
<th>No (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter</td>
<td>23% (7/31)</td>
<td>0% (0/41)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Septic thrombosis synergistic, but did not occur in all cases
Central Vein Catheter-Related Thrombosis in Intensive Care Patients
Incidence, Risks Factors, and Relationship With Catheter-Related Sepsis

- 18-month study period
- 208 central vein catheters (jugular and subclavian)
- Duplex ultrasound performed < 24 hours before catheter removal
- Duration of catheterization: 9 days (mean)
- Catheter-related thrombosis: 33%
  - 42% internal jugular
  - 10% subclavian


Study: 208 central vein catheters

Thrombosis
- Limited: 8%
- Large: 22%
- Occlusive: 3%

Relative Risk
- Internal jugular route: 4.13
- Age > 64: 2.44
- Therapeutic heparinization: 0.44
- Catheter-related sepsis: 2.62-fold higher when thrombosis present


Venous thrombosis in patients with short- and long-term central venous catheter-associated Staphylococcus aureus bacteremias

Purposes
- Determine the incidence of thrombosis in patients with central venous catheter-associated Staphylococcus aureus bacteria
- Utility of physical examination for diagnosing upper-extremity or neck venous thrombosis

Venous thrombosis in patients with short- and long-term central venous catheter-associated Staphylococcus aureus bacteremia

**Methods**

- Prospective, observational study
- 48 consecutive patients with catheter-associated Staphylococcus aureus bacteremia with central venous catheter
- All patients had: Venous duplex ultrasound, Physical examination
- Outcomes assessed at 12 weeks

**Results**

- Thrombosis by US (definite/possible) present in 71% (34/48)
- Death or recurrent bacteremia occurred in 32% (11/34) infected patients with thrombosis
- Death or recurrent bacteremia occurred in 14% (2/14) infected patients without thrombosis
- Sensitivity of physical examination was low: ≤24%
- Only engorged hand veins with elevation and multiple examination abnormalities were specific

**Conclusions**

- Thrombosis is a common complication of catheter associated Staphylococcus aureus bacteremia.
- Patients with Staphylococcus aureus bacteremia should undergo venous ultrasound to rule out thrombosis.
Evaluate the association between catheter-associated bloodstream infection and catheter-associated thrombosis

Purposes

• Retrospective study
• 3.3 years
• 1,540 peripherally inserted catheters
• 882 infants in neonatal ICU

Methods

Number of Infections and Thromboses by Week
Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters

**Results**

**Continued**

- Rate of infection: 13.2/1,000 PIC days
- Rate of thrombosis: 8.9/1,000 PIC days

23/97 (24%) PICs with infection vs. 189/1270 (15%) PICs without infection

...removed for thrombosis ($P < 0.05$)


Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters

**Conclusions**

There is a significant positive association between thrombosis and infection in infants who did not have lines removed ($P < 0.05$).


Infectious Complications of Central Venous Catheters Increase the Risk of Catheter-Related Thrombosis in Hematology Patients: A Prospective Study

Gomez J, van der Meer, Frank A, Hagens, Isagawa M, Armbrust, Hettinger F, Golet, Karda S, de Barrios, and Harnes Y. Harman

**Purposes**

- Assess whether CVC related infection during chemotherapy increased risk of thrombosis
- Assess whether thrombosis can be predicted by CVC lock fluid surveillance

**Methods**

- Prospective study
- 105 consecutive patients
- Examined for CVC thrombosis
- All had microbial surveillance cultures of CVC lock fluid every other day
- Clinical suspicion of thrombosis generated a venous duplex ultrasound

**Results**

- CVC-related infection in 24% (25/105)
- Clinically manifested thrombosis in 12%
- Odds ratio of thrombosis with infection: 17.6%
  - In patients with ≥ 2 positive cultures, thrombosis occurred in 71% of patients (vs. 3% with negative or single positive culture)

**Conclusions**

- Risk of clinically manifest thrombosis increases significantly after CVC-related infection
- Surveillance culturing of CVC lock fluid may be useful
Summary

- Infectious complications do not differ between PICC and CVC lines.
- Thrombotic complications are more significant with PICC and appear earlier after catheterization.
- Prospective data: Approximately 40% of PICC lines will have to be removed before completion of therapy.

CVC: Thrombosis and Infection

Conclusions

- There is a strong inter-relationship between thrombosis and infection.
- Thrombosis significantly lowers the threshold for bacterial colonization.
- Infection stimulates thrombosis.
- Measures to prevent thrombosis will prevent infection.
- Peripherally inserted central vein lines have the same infectious complications and higher thrombotic complications as centrally inserted lines.

Section 2

Clinical consequences associated with UEDVT and impact on patient outcomes:
- Pulmonary embolus
- Paradoxical embolus through patent foramen ovale
- Superior vena cava syndrome (SVT obstruction)
- Post-thrombotic Syndrome (PTS)
- Systemic anticoagulation
Pulmonary Embolus

- **Pulmonary embolism (PE):** blockage of an artery in the lungs by fat, air, a blood clot, or tumor cells

- Difficult to determine the true incidence of PE
  - CR thrombosis is often asymptomatic
  - PE is often asymptomatic (Monreal 1994)
    - More often asymptomatic unless borderline pulmonary reserve (Newsome 2003)

- Embolization of part of mural thrombus
- During withdrawal of CVC, thrombi and fibrin may be stripped from the catheter (Newsome 2003)
  - Generally small; but if respiratory compromise, can create issues or stroke

- Forceful expulsion of intraluminal contents of the CVC by irrigation (Blackburn 1996)

CR subclavian or axillary vein thrombosis is associated with an incidence of PE of up to 12% (Reed 1985)
Background
Upper extremity DVT (UEDVT) is considered to be relatively benign compared to lower-extremity DVT (LEDVT).

Purpose
To study the impact of UEDVT on pulmonary embolism (PE) and mortality compared to LEDVT during the same time period.

Materials/Methods
- Retrospective review
- 18 month-study
- 52 patients with UEDVT
- 430 patients with LEDVT
- V/Q scans performed for clinically suspected PE

Results
Pulmonary Embolism:
- 9 / 52 (17%) with UEDVT
- 33 / 430 (8%) with LEDVT

Mortality in 6 months:
- 48% of UEDVT
- 13% of LEDVT

Conclusions
- UEDVT is associated with higher morbidity/mortality than previously expected.
- UEDVT is an unrecognized predictor of morbidity and mortality.
Paradoxical Embolus

An embolus that passes through a patent foramen ovale

- Thrombus forms in deep venous system
- Can embolize to right atrium
- Then crosses through patent foramen ovale into left atrium
- Travels to brain, producing a non-hemorrhagic stroke

Patent Foramen Ovale (PFO) and Cryptogenic Stroke in Older Patients


Background

- A “probe patent” PFO is present in 27% of the general population at autopsy.
- PFO is greater among patients with “cryptogenic” stroke than among those with stroke of known cause in younger and older patients.
- Among both younger and older patients, PFO is also more prevalent with atrial-septal aneurysm and cryptogenic stroke, as compared to strokes of known cause.

Central venous catheter thrombosis complicated by paradoxical embolism in a patient with diabetic ketoacidosis and respiratory failure

Batesa JA, Craici IM, Froehling DA. Neuroradiol Care 2005;2:185-8

Case Study

- 46-year-old, male in ICU; CVC (central venous catheter) placed in right IJ
- Became unresponsive on day 4; CT showed cerebral infarcts
- Doppler U/S revealed a right jugular venous thrombosis; transesophageal echo revealed patent foramen ovale
- Patient treated with anticoagulants for 3 months; suffered minimal visual and physical disabilities
Case Study

- 61-year-old diabetic male, dual-chamber pacemaker placed
- 6 weeks later presented with confusion, fever, WBC = 18,000; no evidence of pocket infection
- 24 hrs after admission, became lethargic; developed right hemiplegia; CT revealed an embolic frontal hemispheric event
- *Diagnosis by TEE*: Septic paradoxical embolus through PFO due to infected pacemaker lead

Superior Vena Cava Syndrome

- Impedance of blood flow in the SVC either by extrinsic compression or intraluminal narrowing
- Impairs blood flow from the face, neck, upper extremities, and upper thorax

SVC Syndrome: Early Symptoms

- Venous distension upper chest, neck, and face: development of collateral circulation
- Swelling in the face, neck, or upper extremity
- Dry, non-productive cough
- Feeling of “fullness” in the head
- Dyspnea
- Dysphagia
- Chest pain
**SVC Syndrome: Causes**

- Generally caused by cancerous tumors:
  - 87% to 97% of SVCS caused by mediastinal malignancies (Pearl 2002)
  - Lung cancer, lymphoma, breast cancer

- Increasingly common causes:
  - Thrombosis due to CVC or pacemaker placement

**NOTE:** ± 7% of SVCS cases caused by long-term central venous catheters (Pearl 2002)

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**Acute airway obstruction following placement of a subclavian Hickman catheter**


**Clinical Impact: Case Study**

- Patient had history of narrowed SVC, noticed at time of venography
- Hickman placed with tip in SVC
- Immediate severe respiratory compromise requiring intubation
- Catheter removed; symptoms resolved

**Diagnosis:** Acute airway obstruction secondary to SVC obstruction

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**Post Thrombotic Syndrome (PTS)**

A chronic, debilitating complication that occurs after a DVT

- Up to 44% of patients with primary UEDVT
- May occur from 6 to 24 months after DVT diagnosis
- Caused by residual thrombus and valve injury (Elman 2006)

http://www.sonosite.com/healthcare-professionals/imaging/image-gallery/
PTS: Symptoms

- Residual edema, pain, numbness, heaviness in affected extremity
- Results in functional limitations
- Poor quality of life depends on whether dominant vs non-dominant side is affected

Reprinted with permission from Dr. Ezra Steiger, http://www.oley.org/lifeline/Venous_Thrombosis_Associated_with_VADS.htm

PTS: Clinical Impact

- Associated with UEDVT from PICC (Prandoni & Bernardi 1999)
  - 44 patients with PICC-related DVT
  - One-third of patients with UEDVT had mild arm pain
  - One patient with moderate pain
  - No patients reported severe pain

PTS: Clinical Impact (cont’d)

- Meta-analysis of 7 studies by Elman (2005) looked at PTS after UEDVT in adults
- Frequency of PTS after UEDVT: 7% to 46%
- Increased risk of PTS associated with:
  - Axillosubclavian vein thrombosis
  - Residual thrombosis as per ultrasound
- Catheter-associated UEDVT may be associated with a decreased risk
Results

- Daily ipsilateral hand swelling: 52%
- Daily ipsilateral arm pain: 20%
- PTS present in 11 of 25 limbs (44%) and in 11 of 24 patients
- One patient with severe PTS
- When compared with patients without PTS
  - More functional disability
  - Poorer quality of life
- PTS scores were higher and quality of life poorer when PTS was in dominant arm

PTS: Treatment

- Early catheter removal
  - May reduce risk of PTS developing
- Thromboembolism stocking
  - May decrease symptoms in lower-extremity PTS
  - Effect on upper-extremity PTS unknown
- Use graduated compression sleeves for all symptomatic patients
  - May prevent development of chronic venous insufficiency, especially in younger patients

Need for Anticoagulation

Treatment varies for UEDVT

- No intervention
- Removal of catheter
- Removal of catheter and initiation of systemic anticoagulation
- Catheter left in place and systemic anticoagulation initiated

What complications are associated with anticoagulation for thrombosis?
Purpose
To provide reliable estimates of anticoagulant-related bleeding, case fatality rates and intracranial bleeding.

Focus: NON-cancer patients

Data Source
Medline (January 1989 – May 2003)
Cochrane controlled trial registry included:
33 studies with 4,374 patient years of anticoagulation

Results Looking at Incidence of Major Bleed

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>Case Fatality</th>
<th>Rate of Intracranial Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 3 months</td>
<td>2.06%</td>
<td>9.3%</td>
<td>1.48%</td>
</tr>
<tr>
<td>After 3 months</td>
<td>2.74%</td>
<td>9.1%</td>
<td>0.65%</td>
</tr>
<tr>
<td>Entire Period</td>
<td>2.56%</td>
<td>13.4%</td>
<td>1.15%</td>
</tr>
</tbody>
</table>

Anticoagulation Summary for Non-Cancer Patients

- May indirectly increase risk for major bleeding incidence
- Rate of major bleeding may be infrequent
- Death occurs in 10% to 14% of patients who develop a major bleed while on warfarin
Anticoagulation in Cancer Patients

Cancer patients require LMWH due to high incidence of recurrence; however, the complicating factor is occurrence of excessive bleeding.

- As cancer progresses, so do the hazards of anticoagulation
- Associated risks to cancer patients
  - Three-fold higher risk of recurrence of venous thromboembolism
  - Two-fold higher risk of bleeding than patients without cancer

Comparison of Low-Molecular-Weight Heparin vs Oral Anticoagulant Therapy for Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT Study) Lee 2005

“Cancer patients with thrombosis have a shorter life expectancy than cancer patients without thrombosis.”

Purpose
To investigate the overall safety and efficacy of current therapy options to define the optimal treatment strategy specifically for the cancer patient population

CLOT Study Results

Optimal treatment strategy for cancer patients: LMWH for initial event; secondary prevention for a minimal duration of 6 months
### CLOT Study Results (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>LMWH (338)</th>
<th>Wafarin (335)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major S bleed</td>
<td>19 (5.6%)</td>
<td>12 (3.6%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Any S bleed</td>
<td>46 (13.6%)</td>
<td>62 (18.5%)</td>
<td>0.093</td>
</tr>
</tbody>
</table>

* Fisher’s exact test

There was a trend for cancer patients to have more bleeding when anticoagulated; however, it was not statistically significant.

### In Conclusion ...

- Close association between CR thrombosis and infection.
- Upper extremity central vein catheterization is associated with greater PE and mortality than previously expected.
- Individual patient predisposing conditions are impactful as to who develop UEDVT (Patent foramen ovale).
- Thrombosis with malignancy is associated with high morbidity (SVC syndrome).
- Consequences of UEDVT can have life-altering effects on patient outcomes (Post thrombotic syndrome).
- Anticoagulation therapy is not benign.
- Prevention is key.

### Bibliography

Bibliography (cont’d)


Bibliography (concluded)


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